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Salmonella enterica Serotype Choleraesuis: Epidemiology, Pathogenesis, Clinical Disease, and Treatment†

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INTRODUCTION

Salmonella infection of humans and animals continues to be a distressing health problem worldwide. *Salmonella* is a genus of the family *Enterobacteriaceae* (51). Before 1983, the existence of multiple *Salmonella* species was taxonomically accepted. Since then, as a result of experiments indicating a high degree of DNA similarity, all *Salmonella* isolates were classified in a single species, *Salmonella choleraesuis* (42, 51, 135). This species was subsequently subclassified into seven subgroups based on DNA similarity and host range (51, 135). Subgroup I contains almost all the serotypes pathogenic for humans (110, 111, 141).

In 1999, Euzéby proposed to designate "*Salmonella enterica*" as a "neotype species" and replace type species of the genus *Salmonella* from *S. choleraesuis* to *S. enterica* (49), because the name *S. choleraesuis* can lead to confusion since the specific epithet is also the name of a serotype (or serovar). Although this new system of nomenclature has not formally been adopted by the International Committee of Systematic Bacteriology, it has been accepted for use by the World Health Organization and in publications of the American Society for Microbiology. In this review, we write "*S. enterica* serotype Choleraesuis" or "serotype Choleraesuis" rather than "*S. cholearesuis*" to designate a specific serotype for the purpose of continuity with the literature.

The antigenic classification or serotyping of *Salmonella* used today is a result of extensive studies of antibody interactions with bacterial surface antigens by Kauffman and White (85). Three kinds of surface antigens, somatic O antigens, flagellar H antigens, and Vi, determine the reactions of the organisms to specific antisera (85). Specific serotypes were defined as a result of complex antigen variability. This resulted in the identification of over 2,000 *Salmonella* serotypes, most of which were named for the cities where they were defined (85, 97, 110, 111). Although extensive serotyping of all surface antigens can be used for formal identification, most clinical microbiological laboratories perform a few simple agglutination reactions to define specific O antigens into serogroups, designated groups A, B, C1, C2, D, and E (51). This grouping system is useful in epidemiologic studies and can be used clinically to confirm genus identification; however, it cannot quickly identify whether the organism is likely to cause enteric fever, because considerable cross-reactivity among serogroups occurs. For example, serotype Infantis, which typically causes gastroenteritis, and serotype Choleraesuis, a prominent cause of invasive infections, are both group C1. Similarly, serotype Enteritidis, another common cause of gastroenteritis, and serotype Typhi, which causes enteric fever, are both group D.

Among more than 2,000 serotypes, some, such as serotypes Typhi and Paratyphi, are highly adapted to humans and have no other known natural hosts (51, 141). Others, such as serotypes Typhimurium and Enteritidis, have a broad host range and can infect a wide variety of animals (122). Some, such as serotype Choleraesuis (swine) (52, 123, 154), serotype Dublin

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† We dedicate this article to professor Jonathan T. Ou with many thanks.

TABLE 1. The 10 most frequently isolated *Salmonella* serotypes from human sources in the United States and Taiwan[a]

United States, 1999	Taiwan, 1995	Taiwan, 1991–1996
Typhimurium	Typhimurium	Typhimurium
Enteritidis	Choleraesuis	Choleraesuis
Newport	Schwarzengrund	Schwarzengrund
Heidelberg	Agona	Derby
Muenchen	Derby	Haifa
Javiana	Panama	Stanley
Montevideo	Newport	Newport
Thompson	Blockley	Virchow
Oranienburg	Anatum	Paratyphi
Infantis	Infantis	Singapore

[a] Data from references 24, 30, and 32. References 30 and 32 reported the results of two independent investigations from two institutions in Taiwan. The period of collection of the isolates in each study is indicated. The serotypes are listed in order of decreasing frequency.

(cattle) (50), and serotype Arizonae (reptiles) (18, 151), are most highly adapted to a specific animal species but occasionally infect humans. These nontyphoid *Salmonella* serotypes can cause protean manifestations in humans, including acute gastroenteritis, bacteremia, and extraintestinal localized infections involving many organs.

Serotype Choleraesuis is a host-adapted pathogen that causes swine paratyphoid (52, 154). It is also highly pathogenic to humans, usually causing septicemic disease with little involvement of the intestinal tract (19, 39). The resulting serotype Choleraesuis reservoir in swine is a concern, not only because of its disease-causing potential in young pigs but also because of its public health implications for humans (19, 35, 154). Although *Salmonella* is one of the most extensively studied bacterial species in terms of its physiology, genetics, cell structure, development, and host immune response, we are only just beginning to understand at the cellular and molecular levels how serotype Choleraesuis causes invasive infections in humans. This review discusses what is currently known about serotype Choleraesuis. Specific topics discussed include its epidemiology, pathogenesis, genetics, clinical perspectives, treatment, antimicrobial resistance, and vaccines.

EPIDEMIOLOGY

In many countries the incidence of human *Salmonella* infection has increased markedly over the years. In the United States, nontyphoid *Salmonella* serotypes affect approximately 2 million to 3 million persons and cause 500 to 2000 deaths each year (5). In 2000, the two most common serotypes isolated from human sources were *S. enterica* serotype Typhimurium and *S. enterica* serotype Enteritidis (Table 1) (24). *S. enterica* serotype Choleraesuis, including var. *Kunzendorf*, ranked lower than 20th in causing human infections among nontyphoid *Salmonella* strains (24). The annual number of serotype Choleraesuis infections of humans reported to the Centers for Disease Control and Prevention was approximately 80 in 1990 to 1996. The figure decreased gradually thereafter, with an annual number of 49 in 1997, 36 in 1998, 34 in 1999, and 15 in 2000 (24). Serotype Choleraesuis is also an infrequent serotype isolated from human sources in Canada and the United Kingdom (11, 88). However, the epidemiological pattern differed greatly in Asian countries. In Thailand, during 1988 to 1993, serotype Choleraesuis was the 10th most common serotype that caused salmonellosis in humans (8). This highly invasive serotype is of particular concern in Taiwan, since among the common *Salmonella* serotypes isolated from human sources, it was ranked the second in two independent epidemiological surveys (Table 1) (30, 32). A hospital-based surveillance study demonstrated that the average annual number of serotype Choleraesuis infections during 1987 to 2000 was 35 in a 3,500-bed medical center in northern Taiwan (35, 137). The proportion of total *Salmonella* isolates accounted for by serotype Choleraesuis was stable before 1995; however, it decreased from an average of 8.4 to 2.7% in 1996 through 1998 (35, 137). During 1999 to 2000, this proportion increased to an average of 5% (35, 137). The transient decline in 1996 to 1998 was attributed to an outbreak of foot-and-mouth disease in swine, which resulted in an island-wide slaughter of the pigs (35). The study also demonstrated that most of the serotype Choleraesuis isolates from humans and swine exhibited the same or similar DNA fingerprints, indicating that human infections were acquired from pigs (35). We reasoned that the cross-infection arises as a result of contamination of the food or water source by the organism. It is also speculated that the habit of eating pig offal by the local population significantly contributes to the high prevalence of serotype Choleraesuis infection in the locality.

Serotype Choleraesuis is the serotype most frequently isolated from swine; it is rarely isolated from nonporcine reservoirs (24). It causes swine paratyphoid, with clinical manifestations of enterocolitis and septicemia (52, 154). The source of serotype Choleraesuis appears to be limited to carrier pigs and facilities previously contaminated with this serotype (65, 68). The carrier state of serotype Choleraesuis in swine after experimental infection has been described previously (68). Pigs infected with serotype Choleraesuis usually exhibit clinical signs between 36 and 48 h after infection and shed 10^3 to 10^6 CFU of bacteria per g of feces during peak clinical disease (66, 116, 130). Most of the naturally exposed pigs, after recovering from the disease, were able to clear serotype Choleraesuis between 9 to 12 weeks postinfection, indicating that long-term carrier status is an uncommon event (68). Nevertheless, serotype Choleraesuis is able to survive and remain infective in the environment. Shedding of the organism by infected animals can result in long-term environmental contamination and continued reinfection of animals newly introduced in the farms. Furthermore, contaminated environment, food, or water sources can serve as a reservoir for serotype Choleraesuis infection of humans.

In direct contrast to the decrease seen in human infections in the United States, isolations of serotype Choleraesuis from nonhuman clinical sources have increased significantly in recent years (24, 125). The appearance of the porcine reproductive and respiratory syndrome virus (PRRSV), since 1987 has been suggested as one factor that might have contributed to the recent surge of serotype Choleraesuis infections in the United States (125). Serotype Choleraesuis is a highly swine-adapted organism, which can lie dormant in herds until activated by one of several possible stressors. Many secondary diseases, including paratyphoid due to serotype Choleraesuis, have plagued swine herds after a PRRSV outbreak (155). A carrier state of as long as 12 weeks was demonstrated in pigs

infected with serotype Choleraesuis (68). The secondary diseases are thought to be exacerbations of quiescent or subclinical serotype Choleraesuis infections already present in the herds prior to the PRRSV infection; alternatively, subclinically infected pigs may serve as the source of new serotype Choleraesuis infection in repopulated pigs following a PRRSV outbreak (155).

PATHOGENESIS

There have been relatively few investigations of serotype Choleraesuis compared to other *Salmonella* serotypes, such as serotype Typhimurium, in terms of bacterial pathogenesis. Although the infection is associated with a high mortality rate, publications to date on serotype Choleraesuis account for only a small percentage of published studies of *Salmonella* infections. In contrast, considerable work has been described for serotype Typhimurium (4, 28, 44, 53, 56, 59, 83, 91, 93, 95, 101, 108, 115, 139). As a result, we now have a fairly comprehensive understanding of the dominant host defense and protective mechanisms against nontyphoid *Salmonella* infection.

Host Defense

There have been only a few studies that specifically examined host defenses against serotype Choleraesuis. Serotype Choleraesuis is highly host adapted to pigs (52, 154). A pig model of experimental and natural infection of weaning pigs with serotype Choleraesuis has been developed (6). In this model, infection by oral inoculation of 10^8 CFU of serotype Choleraesuis was established, as indicated by an acute illness as well as by recovery of the organism from ileocolic lymph nodes collected at necropsy 7 days postchallenge (6). Serotype Choleraesuis appears to colonize and invade the intestinal epithelium, disseminate to peripheral organs, and cause septicemia in pigs, as does serotype Typhimurium in mice (6, 44, 116). As with serotype Typhimurium, histologically serotype Choleraesuis revealed a predilection for the mucosa of the colon and the luminal surface of ileal M cells of Peyer's patches (113). The invasive capacity of serotype Choleraesuis was also demonstrated by the presence of large numbers of labeled organisms in macrophages in the enteric mucosa as well as in the related lymph nodes (113). Genetically, a cluster of genes controlling the ability of serotype Typhimurium to invade cells in culture and cells lining the intestinal tract of mice has been identified (59). Serotype Choleraesuis also contains the *inv* genes encoding all the invasion functions; however, results of experiments involving knocking out these genes in regard to cell invasion have given ambiguous results (60). In line with this, Finlay et al., who had generated an extensive collection of serotype Choleraesuis mutants which had been screened for cell infectivity, never found any mutant with specific invasion defects (54). This indicates that serotype Choleraesuis might possess a unique means, not exhibited by serotype Typhimurium, of being invasive.

The immune response to serotype Choleraesuis was also investigated by using a swine or mouse challenge model. Both cellular and humoral immune activation occur after oral inoculation (67). Antibody response to both lipopolysaccharide and outer membrane protein antigens in pigs following an oral challenge of 10^8 CFU of serotype Choleraesuis has been documented (133). Such doses also result in the development of a long-term carrier state in pigs (66, 133). The carrier state existed despite the presence of antibody and a measurable cellular response to serotype Choleraesuis antigens (66, 133). It was suggested that the immune system of pigs may be overwhelmed by a challenge with such a large dose of bacteria (66). At moderate doses, between 10^3 and 10^7 CFU, antigen stimulation of lymphocytes was optimal and mitogenic responses remained normal (66). Cellular immunity is thought to be essential to overcome infections with facultatively intracellular pathogens such as *Salmonella*. This concept was described by Mackaness and colleagues who first established the relationship between infection with intracellular pathogens of macrophages and induction of the host response that was mediated by activation of macrophages by T cells and their secreted products (94). We now know that the T cells involved in this pathway are of the T-helper 1 (Th1) phenotype and that gamma interferon (IFN-γ) is the T-cell product that is primarily responsible for macrophage activation (103). There have been only a few animal or in vitro studies that provide some indication of the importance of cellular immunity in host defense against serotype Choleraesuis. Foss et al. demonstrated that both in vivo and ex vivo infection of the intestinal mucosa with serotype Choleraesuis resulted in a decrease in the amount of interleukin-18 (IL-18), which is consistent with cleavage of the preprotein by caspase-1 (55). IL-18 is a cytokine that has structural and functional similarities to IL-12; it induces the secretion of IFN-γ and was originally identified in mice as an IFN-γ-producing factor. This suggests that the caspase-1 activation of IL-18 may be an important step in mucosal immunity to serotype Choleraesuis infection. The role of another cytokine, IL-15, in protection against serotype Choleraesuis was also investigated by Hirose and colleagues using mice depleted of IL-15 by administration of anti-IL-15 antibody (80). The results indicated that IL-15 may be involved in protection at early stages of infection through activation of NK cells at infected sites (80). Furthermore, the use of mice deficient in γδ T cells showed that these cells play an important role in the pathogenesis of lethal infection with serotype Choleraesuis (47, 48). Excessive tumor necrosis factor alpha production, which is often detrimental in the pathogenesis of gram-negative bacterial infection, is not evident in γδ T-cell-deficient mice after infection, and this phenomenon may be at least partly ascribed to the resistance of such mice to lethal serotype Choleraesuis infection (48). Interestingly, most of the studies mentioned above were performed using avirulent strains of a serotype Choleraesuis. These strains were cured of a 50-kb virulence plasmid (pSCV) and had high 50% lethal doses for mice. Hence, it was postulated that a plasmid-borne virulence factor may impair the cellular immune response to serotype Choleraesuis; on the other hand, cytokines in the Th1 pathway had an important function in protection against infection with plasmidless, avirulent strains of serotype Choleraesuis accompanied by increases in NK-cell and IFN-γ production. The plasmid-associated immunosuppression may have important implications in the development of a vaccine to prevent serotype Choleraesuis infection in farm pigs.

The nature of the interaction of various *Salmonella* serotypes with porcine macrophages was studied using pigs as the

infection model (7, 152). Serotype Choleraesuis can survive, multiply, and even establish bacteremia after being ingested by macrophages (7). Persistence of *Salmonella* organisms within porcine macrophages seems not to directly correlate with their virulence to pigs. In other words, serotype Choleraesuis is highly virulent to pigs but persists in smaller numbers than does serotype Typhimurium. This appears to support a recent observation that the serotype-host specificity of serotype Choleraesuis does not correlate with invasion of the porcine intestinal mucosa (20). The interaction of serotype Choleraesuis with porcine polymorphnuclear leukocytes (PPMN) has been well characterized in vitro. PPMN readily killed either virulent or avirulent serotype Choleraesuis strains; however, the virulent serotype Choleraesuis strains survived PPMN killing more effectively than did the avirulent ones (121). Interestingly, the functions of PPMN were markedly suppressed in the presence of virulent and avirulent serotype Choleraesuis strains (121). Both strains appeared to have similar capabilities to either prevent degranulation or inhibit H_2O_2 production (121); however, only the virulent serotype Choleraesuis strain significantly reduced ingestion of *Staphylococcus aureus* by PPMN (121). The exact mechanisms behind these observations remain unclear.

Bacterial Genetics

In an analysis of *Salmonella* genomes by microarray techniques using the genome of serotype Typhimurium LT2 as a standard, approximately 90% of the annotated LT2 open reading frames (ORFs) were homologous among members of all seven subgroups (112). Comparative genomic analysis of serotypes Typhimurium and Typhi (full genome sequences), and serotypes Dublin, Enteritidis, and Paratyphi (draft sequences) revealed that in each genome approximately 10 to 12% of unique DNA was acquired by horizontal gene transfer (96, 109). Most of these acquired regions are related to the pathogenicity islands by insertion into tRNA genes (78). *Salmonella* pathogenicity islands contain virulence genes and regulatory elements in addition to those encoding specialized protein secretion systems known as type I and III secretion systems (96). In addition, a few serotypes of *Salmonella*, including serotype Choleraesuis, carry a virulence plasmid that is involved in the pathogenesis of the organism in its natural host.

Virulence plasmids. Subgroup I *Salmonella* serotypes include 1,454 serotypes and at least 99% of clinical isolates (110, 111, 141). Only a few of these serotypes harbor a virulence plasmid which carries the *spv* operon (34, 73, 74). The size of these plasmids varies with each serotype, ranging from 50 to 285 kb (73, 74, 107). The *spv* operon is required for the systemic phase of disease in specific hosts with specific virulence plasmid size, i.e., serotype Choleraesuis with a 50-kb virulence plasmid in pigs (43), serotype Dublin with an 80-kb virulence plasmid (pSDV) in cattle (92, 149), serotype Gallinarum with an 85-kb virulence plasmid (pSGV) and serotype Pullorum with an 85-kb virulence plasmid (pSPV) in fowl (12, 13), serotype Typhimurium with a 95-kb virulence plasmid (pSTV) and serotype Enteritidis with a 60-kb virulence plasmid (pSEV) in mice (74, 84), and serotype Abortusovis with a 95-kb virulence plasmid (pSAV) in sheep (146).

TABLE 2. Major differences in operons or genes among virulence plasmids

Operon or gene[a]	Operon present in:					Function
	pSTV	pSPV	pSDV	pSEV	pSCV	
rsk	+	−	−	+	+	Serum resistance
repA of RepFIB	+	−	−	+	+	Replication
pef opereon						Biosynthesis of fimbriae
pefBACD	+	−	−	+	+	
orf5	+	−	−	+[b]	−	
orf6	+	−	−	+[b]	−	
faeHI	−	+	+	−	−	Biosynthesis of fimbriae
rck	+	+	+	+	−	Serum resistance
traT	+	+	+	−	+	Serum resistance
oriT	+	+	−	+	−	Mobilization

[a] Arrangement according to genetic order described previously (37).
[b] DNA sequence differs from that of pSTV (77).

The complete nucleotide sequences of pSCV (pKDSC50) of serotype Choleraesuis RF1 and pSTV of serotype Typhimurium LT2 have been determined. The 49,503-bp pSCV contained 48 ORFs (43, 77), and the 93,939-bp pSTV contained 108 ORFs molecules (96). Comparison of the two plasmids reveals that they are closely related (37, 38). In fact, all the *Salmonella* virulence plasmids show a very close relationship. A heteroduplex analysis indicates that the level of closeness runs, in descending order, from pSTV to pSEV to pSCV to pSDV (102). Analysis of the major variations in serum resistance genes *rsk* (for "resistance to serum killing"), *rck* (for "resistance to complement killing"), and *traT* and the minor fimbria genes, *pef*, *faeH*, *faeI*, and *oriT* suggested the existence of at least two groups of virulence plasmids. Group I includes pSDV and pSPV, which contain *faeH* and *faeI* without *rsk*, *repA* of RepFIB, and *pef;* in contrast, group II includes pSTV, pSEV, and pSCV, which contain *rsk* and *repA* of RepFIB and *pef* but no *faeH* and *faeI* (37, 38). In comparison to the nucleotide sequence of pSTV, two large deletions of the *pef* operon and the *tra* region are found in pSCV (37), suggesting that pSCV is derived from pSTV by deletions. The major differences in operons or genes among the various virulence plasmids are summarized in Table 2.

Serum resistance genes *rck*, *rsk*, and *traT* are present in most of the virulence plasmids. The *rck* gene encodes an outer membrane protein, homologous to PagC (for "*phoP*-activated gene") (76) and Ail (for "attachment and invasion locus") (100), which conferred host serum resistance. The *rsk* gene is only 66 bp long and contains a series of direct 10-bp repeat in the 5′-noncoding region of the *repA* gene of RepFIB (148). In addition, a gene, *spf* (for "stimulation of protein forty"), near *rsk* was recently found to be involved in the production of IL-12 p40 in *Salmonella*-infected macrophages (25). The *traT* gene encodes a surface lipoprotein homologous to the product of the *traT* surface exclusion gene located on plasmid F and F-like conjugation systems. The introduction of the *traT*-containing plasmid appears to be responsible for the slight increase in serum resistance of rough serotype Typhimurium strains (119). In comparison with other virulence plasmids, apparently pSCV lacks *rck* but contains *traT* (Table 2).

Adhesins are known to support the colonization of *Salmonella* in the host alimentary tract, thereby increasing the bac-

terial load in the vicinity of the epithelial cell lining. The *pef* operon is a 7-kb region containing genes for plasmid-encoded fimbriae (57). It includes the *pefBACD*, *orf5*, *orf6*, and *pefI* genes (57). It has been documented that the *pef* fimbriae mediate bacterial adhesion to murine intestinal epithelium, resulting in fluid accumulation in the gut (17). pSCV has a deletion in the region behind *pefD* (37), and pSEV has sequence variations in *orf5* and *orf6* (77). These deletions and variations of *orf5*, *orf6*, and *rck* may be associated with host adaptation in *Salmonella*.

All virulence plasmids contain two virulence factors, *mig-5* and the *spv* operon. The *mig-5* gene is important for bacterial colonization in the mouse spleen (147). The *spv* operon consists of four structural genes, *spvABCD*, and a positive regulatory gene, *spvR* (71, 73, 75). The *spv* genes are induced during different stresses, including starvation and the stationary phase of growth (72), and within host cells (118, 156). The expression of *spv* genes is positively regulated by SpvR, the product of *spvR* (2), and is enhanced at stationary phase under the control of sigma factor RpoS (σ^{38}) but is repressed by the SpvA (1).

Evolution of the serotype Choleraesuis virulence plasmid. As mentioned above, serotype Choleraesuis usually harbors a pSCV plasmid of 50 kb. Recently, however, several serotype Choleraesuis isolates from humans and pigs that harbored various numbers as well as sizes of plasmids were isolated (36). The 50-kb plasmids are all pSCV since they all carry a *spv* operon, and the larger plasmids, ranging from 125 to 140 kb, were also shown to carry a *spv* operon; hence, they were all pSCVs (36). The results of PCR with primers flanking two specific deletion regions, *orf5-repA* of RepFIIA and *traT-samA* (36), confirmed that these large pSCVs were indeed derived from the 50-kb pSCV. These large pSCVs also contained additional DNA from other 75- and 90-kb plasmids. Most of the clinical isolates were resistant to multiple antimicrobial agents (36). We found that at least two resistance genes, *sul* and $bla_{\text{TEM-1}}$, which were responsible for resistance to sulfonamide and ampicillin, respectively, were present on the large pSCVs. These genes on the large pSCVs were apparently acquired through recombination. The acquisition of resistance genes by pSCV constitutes a new and interesting example of plasmid evolution and presents a serious public health problem. Biologically, the larger size of pSCV may not have any advantage, except that the process of its formation is probably the means by which pSCV acquires drug resistance, an advantage in an unfavorable drug environment.

CLINICAL SPECTRUM OF INFECTION

Nontyphoid *Salmonella* serotypes are major causes of foodborne infections worldwide. They still seriously affect human health and cause morbidity and mortality. Infections with nontyphoid *Salmonella* serotypes most often result in self-limited acute gastroenteritis that does not require antimicrobial therapy. Nevertheless, approximately 5% of individuals with gastrointestinal illness caused by nontyphoid *Salmonella* serotypes develop bacteremia. Children with certain underlying conditions are at increased risk of bacteremia, which may lead to extraintestinal focal infections. Such conditions include very young age (babies), AIDS, malignancies, immunosuppressive therapy, hemolytic anemia, and inflammatory bowel disease (29, 32, 39, 129). Nontyphoid *Salmonella* bacteremia is even more serious in adult patients with underlying diseases; these patients are more likely to develop focal infections such as meningitis, septic arthritis, and osteomyelitis. Certain serotypes of *Salmonella*, i.e., serotypes Choleraesuis and Dublin, show a much higher predilection for causing bacteremia in humans (29, 31–33, 39, 143). These serotypes rapidly invade the bloodstream with little or no intestinal involvement. In Taiwan, serotype Choleraesuis has the highest invasiveness (measured in terms of invasion index, which is the number of extraintestinal isolates divided by the total number of isolates) (31–33). In England and Wales, while the largest numbers of bloodstream isolates were from infections caused by serotypes Typhimurium and Enteritidis, the highest incidence of sepsis, also based on the invasion index of each individual serotype, was attributable to infections with serotypes Choleraesuis, Dublin, and Virchow (143). A recent retrospective analysis of adult patients with serotype Choleraesuis bacteremia showed that most of the patients had obvious risk factors for salmonellosis, including malignancy, liver cirrhosis, systemic lupus erythematosus, and previous use of corticosteroids (29). It was notable that 21% of the bacteremic patients subsequently developed focal infections, including septic arthritis, pneumonia, peritonitis, and cutaneous abscess (29). This reflects both the tenacity of serotype Choleraesuis and the comorbidities of the adult patients who develop bacteremia.

A feared complication of *Salmonella* bacteremia in adults is the development of infectious endarteritis (also known as infectious aortitis or mycotic aneurysm). The description "mycotic aneurysm" originated early in 1885 and was coined by Osler (106). It was originally used to describe the septic emboli seen in patients with infective endocarditis. These embolic materials are carried by the blood flow to distal arterioles, where they cause obstruction or attach to the vessel walls. Inflammation and subsequent destruction of the involved vessels ensue, leading to the formation of a mushroom-shaped aneurysm. However, most people think that "mycotic" simply referred at that time to any infection caused by microorganisms and was only later restricted to fungi. In 1986, Sheng and Busuttil classified these aneurysms into five categories, one of which is caused by secondary infection in patients with bacteremia and with underlying atherosclerosis or severely damaged arterial walls (127). Nowadays, the use of the term "mycotic aneurysm" implies a wide spectrum of disease entities including all cases of true or pseudoaneurysms. Most of the patients with mycotic aneurysm due to *Salmonella* have preexisting atherosclerotic disease at the site of subsequently infected aneurysm (40, 105). In a series of patients with bacteremia due to *Salmonella*, 25% of those older than 50 years developed an endothelial infection (40). This reflects the ability of *Salmonella*, which has been reported to invade normal arterial intima, to cause endothelial infection in the presence of atherosclerosis (40). The predominance of older patients with or without hypertension among patients with *Salmonella* aortitis is probably due to the increased incidence of atherosclerosis and intimal damage in these patients. Recently, *Salmonella* bacteremia has been noted in patients with human immunodeficiency virus infection; however, aortitis rarely occurs in these patients because they are relatively younger and do not have the above risk factors (99). Unfortunately, most of the

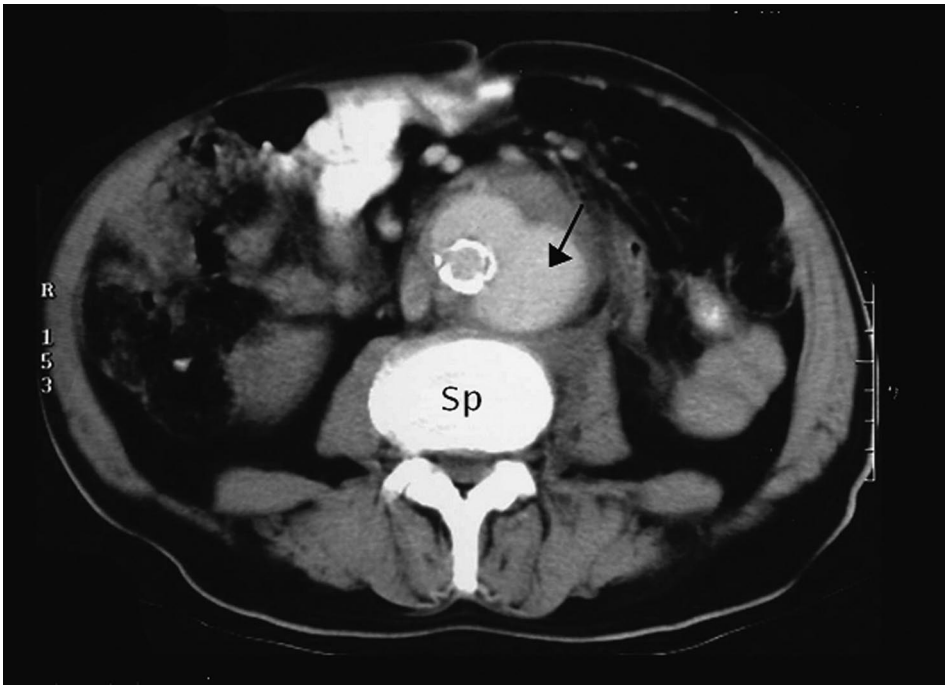

FIG. 1. Axial CT scan of the abdomen of a patient with *S. enterica* serotype Choleraesuis infection, depicting a periaortic mass with intimal rim enhancement (arrow). Abbreviation: Sp, spine.

data on risk factors were from anecdotal reports or retrospective reviews; consequently, the precise risk factors remain unclear. A prospective case-control study is urgently called for.

According to a review of 140 cases of aortitis due to *Salmonella* reported in the literature since 1948, the most common site of infection is the abdominal aorta, more precisely its infrarenal portion (131). The most common clinical features consisted of fever, abdominal pain, and/or back pain, the last of which may be related to the site of involvement (131). A computed tomographic (CT) scan with contrast enhancement is considered the method of choice to diagnose mycotic aneurysm because of its ability to detect early changes in the arterial wall and the periaortic tissue (63, 131). These changes include a periaortic soft tissue density with rim enhancement (Fig. 1), an eccentric, thickened wall with rapid growth, lack of calcium in the aneurysmal wall of the aorta, and gas in the perianeurysmal soft tissue (63). Angiography may subsequently be performed for confirmation of the diagnosis or assistance in planning future surgical procedures. However, angiography is invasive and does not detect the early changes produced in the arterial wall or in the periaortic tissue. It may be virtually contraindicated because of the risk of aneurysmal rupture. Magnetic resonance (MR) imaging, on the other hand, provides the most safe and accurate technique for diagnosis. An understanding of the principles underlying the appearance of flowing blood on MR images has led to the development of MR angiography, in which a clear display of vascular anatomy is generated. The use of MR angiography has particular appeal for diagnosing mycotic aneurysm since it is entirely noninvasive and does not require the use of intravenous contrast material or ionizing radiation. MR angiography produces images in the transverse, sagittal, and coronal planes, which display the entire thoracic or abdominal aorta in one plane. The availability of these multiple views facilitates the diagnosis of mycotic aneurysm and the determination of its extent and in many cases reveals the presence of branch vessel involvement (27, 131, 150). Figure 2 shows an MR angiogram of a patient with a mycotic aneurysm at the infrarenal portion of the abdominal aorta.

Mycotic aneurysm caused by *Salmonella* was almost uniformly fatal in previous times; however, multiple publications of case reports and case series found that early surgical intervention has greatly increased survival (3, 27, 63, 105, 131, 142, 150). Most surgeons consider the excision of an infected vessel with extra-anatomic vascular reconstruction to be the surgery of choice for abdominal mycotic aneurysm (142). In addition, a prolonged course of antibiotics (for 6 weeks or longer) is indicated (3, 40, 150). A recent review of 136 evaluable cases in patients seen from 1948 through 1999 found a 62% survival rate (38% mortality) for all such patients treated with combined surgical and medical therapy (131). This improved survival was apparently due to the use of advance diagnostic techniques, surgical care, and antimicrobial therapy.

In literature reviews of *Salmonella* aortitis, the serotypes most commonly isolated were serotypes Typhimurium, Enteritidis, and Choleraesuis, in decreasing order (127, 131). Overall, around 30% of the reported patients was infected by serotype Typhimurium and 15% each were infected by serotypes Enteritidis and Choleraesuis (131). Interestingly, the reports of a relatively high incidence of serotype Choleraesuis infection came mostly from Taiwan (27, 150). In Taiwan, serotype Choleraesuis was the second most common serotype among all *Salmonella* serotypes isolated and showed the greatest ability to cause extraintestinal infections (32, 33). The high virulence

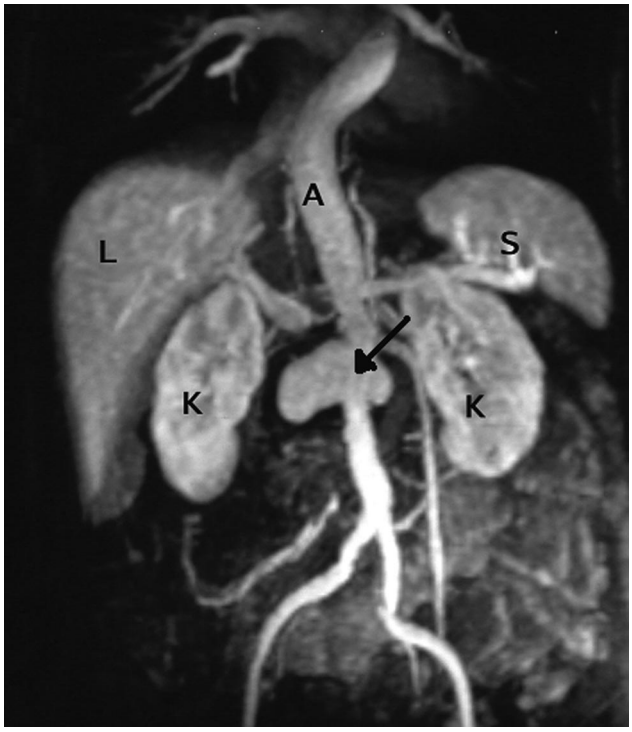

FIG. 2. Coronal MR angiogram of a patient with *S. enterica* serotype Choleraesuis infection, revealing aneurysm formation (arrow) at the infrarenal portion of the abdominal aorta. Abbreviations: A, aorta; K, kidney; L, liver; S, spleen.

of serotype Choleraesuis to humans, as well as its high prevalence, may have contributed to the high incidence of endovascular infection caused by this organism in Taiwan.

TREATMENT

Antimicrobial agents should not be used routinely to treat uncomplicated nontyphoid *Salmonella* gastroenteritis. However, antimicrobial therapy is essential in the treatment of serotype Choleraesuis infection, in view of the high rate of extraintestinal infections caused by this organism. Because of the increasing prevalence of resistance to conventional antimicrobial agents (see below), such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, empirical therapy for life-threatening bacteremia or focal infection suspected to be caused by nontyphoid *Salmonella* should include a broad-spectrum cephalosporin or a fluoroquinolone until susceptibility patterns are known. It is also important to search for endovascular abnormalities by using imaging techniques in older patients with or without evidence of atherosclerosis. Although there is no consensus on the optimal duration of postoperative antibiotic therapy for endovascular infections caused by *Salmonella*, most investigators still recommend a minimum of 6 weeks (3, 39, 40, 150). The duration of therapy for other extraintestinal infections should be considered based on the site of infection. In general, 10 to 14 days for bacteremia, 4 to 6 weeks for osteomyelitis, and 4 weeks for meningitis are suggested. Prolonged therapy may be needed in immunocompromised patients. Many consultants would prescribe some months of suppressive therapy, following parenteral treatment, especially for human immunodeficiency virus-infected patients. For patients with a focal suppurative process, surgical drainage should be undertaken as soon as possible in addition to antibiotic treatment for the best chance of achieving a cure.

ANTIMICROBIAL RESISTANCE

Epidemiology

Antimicrobial resistance among nontyphoid *Salmonella* serotypes has been a serious problem worldwide (35, 41, 81, 117, 124, 137, 140). Conventional antimicrobial agents, such as ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, had been the drugs of choice in the treatment of salmonellosis before the 1980s. However, multidrug resistance, with rates of resistance to these antimicrobial agents of more than 50%, has been reported in many areas of the world (35, 45, 124, 137). Extended-spectrum cephalosporins and fluoroquinolones have been suggested as appropriate alternative agents in the treatment of infections caused by such multidrug-resistant *Salmonella* serotypes (10, 22, 64); however, since 1991, outbreaks or cases of infections caused by *Salmonella* serotypes resistant to extended-spectrum cephalosporins or fluoroquinolones have been increasingly reported (9, 16, 21, 23, 35, 61, 62, 90, 114, 128).

As to serotype Choleraesuis, probably due to a relatively lower prevalence rate, reports of antimicrobial susceptibility in the western countries are rare. Nevertheless, a number of reports from Taiwan have indicated a worrisome situation that this highly invasive serotype has expressed high-level resistance to antimicrobial agents (29, 30, 35, 36, 137, 138). A report described the secular trend of antimicrobial resistance to the conventional antibiotics in serotype Choleraesuis isolates from a university hospital in Taiwan (35), showing that the rate of resistance to ampicillin, chloramphenicol, or trimethoprim-sulfamethoxazole had increased to around 90% for all three drugs in 2000 (35). Veterinary studies also demonstrated a high rate of chloramphenicol resistance (MIC for 90% of strains [MIC_{90}] > 128 μg/ml) in serotype Choleraesuis strains isolated from swine (26). Moreover, in 2000 we observed the emergence of resistance to ciprofloxacin in serotype Choleraesuis in Taiwan (35); the resistance rate increased to 59% in 2002. As to the extended-spectrum cephalosporins, for the first time a ciprofloxacin-resistant serotype Choleraesuis isolate was found to express an intermediate level of resistance (MIC = 16 μg/ml) to ceftriaxone in 2002 (34a). Imipenem became the last and only effective antimicrobial agent in such circumstances to treat infections caused by the multidrug-resistant serotype Choleraesuis strain. In view of the serious implications arising from these situations, the chain of transmission and mechanism of resistance should be carefully studied to reduce the spread of resistance and its threat to human health.

Spread of Resistance

The emergence of antimicrobial resistance in *Salmonella* is complicated because the use of antibiotics for therapeutic purposes in veterinary medicine and as growth promoters in ani-

mal feed may promote the emergence of resistance, thus presenting a potential risk to public health from zoonotic infections (35, 82, 132). In addition, pet animals such as frogs and turtles and their water environment were shown to carry multidrug-resistant *Salmonella* strains (126, 145), which could subsequently cause infections in humans. For serotype Choleraesuis, results of molecular epidemiological surveys indicated that swine serve as the prime reservoir for resistant serotype Choleraesuis strains (35). To curb the resistance problem in *Salmonella*, it has been suggested that inappropriate use of antimicrobial agents in food animals should be prohibited (35, 153).

Mechanisms of Resistance

Some studies pointed out the serious problem that several *Salmonella* serotypes, including serotype Choleraesuis, could generate different types of hybrid plasmids, which consisted of the serotype-specific virulence plasmid and an array of gene cassettes (36, 69, 70, 93). Most of the gene cassettes contained resistance genes that were responsible for resistance to conventional antibiotics, such as ampicillin, chloramphenicol, gentamicin, oxacillin, spectinomycin, streptomycin, sulfadiazine, tetracycline, trimethoprim, and other materials, including ammonium antiseptics and mercury (36, 69, 70, 93).

A rapid emergence of resistance to ciprofloxacin has been reported in serotype Choleraesuis recently, and all of the resistant strains were shown to have mutations that gave rise to the substitution of phenylalanine for serine at position 83 and asparagine for aspartic acid at position 87 in GyrA (35). In addition, mutations in *parC* leading to an amino acid change from serine to isoleucine at position 80 were found in most of the ciprofloxacin-resistant serotype Choleraesuis isolates (C. H. Chiu, unpublished data). Further studies are required to determine whether active-efflux pumps are also involved in fluoroquinolone resistance phenotype in serotype Choleraesuis.

Resistance to broad-spectrum cephalosporins is due to the production of extended-spectrum β-lactamases. A variety of such β-lactamases have been described in *Salmonella*, most of which are cefotaxime-hydrolyzing β-lactamases (CTX-M types) (9, 16, 21, 61, 62, 114, 128) or CMY-2 AmpC β-lactamases that could hydrolyze cephalosporins as well as cephamycins (23, 90). The genes encoding extended-spectrum β-lactamases could be carried by conjugative plasmids, transposons, or integrons. These mobile genetic elements could spread, under selective antibiotic pressure, between bacterial species (23, 58, 134).

There have been no such reports regarding the resistance of serotype Choleraesuis to the extended-spectrum cephalosporins in the literature. However, we have recently isolated a CMY-2-producing serotype Choleraesuis strain that expressed intermediate-level resistance to ceftriaxone. The $bla_{\text{CMY-2}}$ of this isolate was carried by a 140-kb F-like plasmid. In addition, a class 1 integron with a gene cassette carrying *dfr* and *aadA2* genes was found on both the chromosome and the 140-kb plasmid of this isolate (34a). Since the strain also expressed resistance to ciprofloxacin, carbapenem became the only agent available for effective treatment (89). A feared fact is that *Salmonella* isolates with resistance to imipenem have already been reported early in 1997 (46).

Clinical Relevance

The association between antimicrobial resistance and salmonellosis has several facets (14, 15, 144). The most important appears to be its impact on the treatment of infections. Patients with invasive salmonellosis require effective antimicrobial therapy. Growing antimicrobial resistance may add to the difficulty in treating patients with such infections, thus leading to increased morbidity and mortality (98). Many previous reports have provided evidence of this development for other antimicrobial-resistant *Salmonella* serotypes (79, 136). Although no similar developments have been reported for serotype Choleraesuis, it may be expected that the situation would be worse in this case because serotype Choleraesuis usually causes invasive infections that require antimicrobial therapy.

Another impact of antimicrobial resistance on human and veterinary medicine is the linkage of virulence traits and resistance genes, which implied that resistant strains may be more virulent than susceptible strains (14, 144). Epidemiological reports have indicated that antimicrobial-resistant strains of *Salmonella* could cause more prolonged or more severe illness than do susceptible strains (144). A previous molecular study demonstrated that serotype Choleraesuis could become resistant to multiple antibiotics by acquiring drug resistance genes through recombination of the virulence plasmid and the resistance plasmid (36). Such plasmid-mediated antimicrobial resistance could provide virulent *Salmonella* with the advantage of causing infections in an unfavorable drug environment, leading to increased mortality in patients or infected animals.

VACCINE

Nontyphoid *Salmonella* serotypes causing gastroenteritis in humans are most often transmitted through the food chain by contamination of poultry and eggs, pork, beef and dairy products, and, increasingly in the United States by vegetables and fruits that are irrigated with *Salmonella*-contaminated water (98). The question that had been posed by investigators many years ago is whether vaccination would be a feasible approach when combined with improved management practices for the control of *Salmonella* in poultry, swine, and cattle to lessen the likelihood of *Salmonella* transmission through the food chain to humans. In other words, could vaccines to prevent the infection and colonization of animals with *Salmonella* contribute to the safety of food? One difficulty in attaining such a goal is the probably correct assertion that most *Salmonella* serotypes that colonize animal species and that are passed through the food chain to humans are essentially members of the normal flora of these animals and do not often cause disease. Hence, the design of any efficacious vaccine to block colonization of or infection by "normal flora" constitutes a difficult task.

Proven means of attenuation of serotype Typhimurium for mice did not yield a protective vaccine when used to attenuate serotype Choleraesuis. This included using *aro*, *galE*, and *cya-crp* mutations (86, 104). In an attempt to attenuate serotype Choleraesuis some years ago, Curtiss and colleagues discovered the *cdt* locus adjacent to *crp* and found that a serotype Choleraesuis strain with the Δ*cya* and Δ*crp-cdt* double mutations was avirulent and immunogenic in mice (86). In the United States, there are three licensed serotype Choleraesuis

vaccines for swine. The Arco serotype Choleraesuis vaccine was derived by chemical mutagenesis, but the basis of attenuation is not very well understood. The Nobl vaccine was passaged through neutrophils and lost its virulence plasmid, which is the principal attenuating defect (120). Argus-SC, which is distributed by Bayer but was originally developed by Upjohn, has the Δ*cya* Δ*crp-cdt* mutations. In studies at Upjohn, young pigs were immunized with the Bayer Argus-SC vaccine and challenged, nonvaccinated and challenged, or not challenged (87). There was significant morbidity after challenge in animals that were not vaccinated and a high degree of diarrhea. Since the animals were about 6 weeks of age, there was no mortality, but the pigs continued to shed the challenge strain a week after challenge. There was also a significant increase in body temperature compared to the control nonvaccinated, nonchallenged pigs. Pigs vaccinated with the Nobl vaccine, which lacks the virulence plasmid, had higher temperatures and diarrheal scores with more *Salmonella* shed in feces after challenge than was the case in pigs immunized with the Δ*cya* Δ*crp-cdt* vaccine. Both groups of immunized pigs performed better than the nonimmunized challenged pigs and showed better weight gains. None of these vaccines for swine have been introduced in Europe (except Germany) or other parts of the world.

It is concluded that the most logical means of diminishing the transmission of *Salmonella* through the food chain to humans would be to vaccinate farm animals on a routine basis with live attenuated *Salmonella* vaccine. The problem is that other than Germany, there is no requirement to do so in any other part of the world. Agriculturally important animals are commodities, and therefore producers are not willing to invest in the cost of a vaccine and a vaccination program unless they are required to do so or unless failure to vaccinate results in a severe problem, such as being unable to market their products. In this regard, it is permissible in the United States to have up to 20% of broiler carcasses fecally contaminated with *Salmonella* at the time of slaughter. Therefore, although the means for using vaccination to contribute to the improvement of food safety exists, it will take education and a change in government policies to bring that about.

CONCLUSIONS

S. enterica serotype Choleraesuis usually causes systemic infections without overt gastroenteritis in humans. In comparison with other highly prevalent serotypes of *Salmonella*, such as serotypes Typhi, Typhimurium, and Enteritidis, this organism has received much less attention; therefore, not surprisingly, our knowledge of it is not only incomplete but also significantly lacking. With serotype Choleraesuis being increasingly recognized as a problematic cause of systemic salmonellosis in Asian countries, additional prospective studies of host risk factors and of important virulence factors are needed. A major issue is the management of serotype Choleraesuis infections. The emergence of serotype Choleraesuis that is resistant to ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, and, notably, fluoroquinolone antibiotics has aroused concern about the use of these agents for the empirical treatment of systemic infection caused by this organism. In view of the serious implications of this situation, the chain of transmission and mechanism of resistance should be studied to reduce the spread of resistance and its threat to human health. On the other hand, advanced tools are now in hand to further elucidate the pathogenesis of serotype Choleraesuis at a molecular level. To obtain a global view of genes possessed by serotype Choleraesuis and to solve the worrying clinical problems, we propose that the genome of serotype Choleraesuis should be sequenced. Understanding the genome sequence of serotype Choleraesuis may facilitate the development of effective vaccines as well as the identification of new targets for novel antimicrobial agents. In any event, if serotype Choleraesuis infections are to be adequately controlled in the future, comprehensive studies of their epidemiology, pathogenesis, genetics, and resistance must be performed.

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